Thermolabile Methylenetetrahydrofolate Reductase Polymorphism (C677T) and Total Homocysteine Concentration Among African American and White Women.

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Abstract

A polymorphism associated with a thermolabile variant (C677T) of the enzyme methylenetetrahydrofolate reductase has been associated with both elevated total homocysteine (tHcy) levels and risk for cardiovascular disease. Data from the Stroke Prevention in Young Women Study were used to determine the prevalence of the C677T genotype and to assess whether environmental factors modified the association between genotype and tHcy concentration. The C677T genotype prevalence was 80% -/-, 20% +/-, and 0% +/+ among 46 African American women and 39% -/-, 53% +/-, and 8% +/+ among 77 white women (P<0.01). There was a trend towards higher tHcy levels in African American women with the +/- genotype when compared with the -/- genotype (6.9 µmol/L vs. 5.3 µmol/L respectively, p=0.10); no association was found among the white women (6.0 µmol/L, -/-; 4.5 µmol/L, +/-; and 6.2 µmol/L, +/+; p=0.67) . Among African American women, those who smoked and were +/- genotype had the highest tHcy levels (8.0 µmol/L); while among white women, those who smoked and were -/- had the highest tHcy levels (8.1 µmol/L). Despite being hampered by a limited sample size, the thermolabile allele is significantly less common among African American than white women. The association between genotype and tHcy concentration is influenced by smoking and multivitamin use.

Introduction

Elevated total homocysteine (tHcy) levels have been identified as a risk factor for coronary artery disease,[1-6] stroke,[7-9] and peripheral vascular disease.[10-11] In a meta-analysis investigating the association between tHcy and coronary artery disease, Boushey et al. reported that a five µmol/L increase in tHcy was associated with an odds ratio of 1.6 in men and 1.8 in women.[12] tHcy levels are modulated by the interaction between a number of nutritional and genetic factors; including folic acid, vitamin B12, and vitamin B6.[13,14] Approximately two-thirds of elevated tHcy levels may be secondary to low or moderate levels of these B vitamins.[13]

The enzyme methylenetetrahydrofolate reductase (MTHFR) reduces 5',10'-methylenetetrahydrofolate to 5'-methyltetrahydrofolate, a substrate in the remethylation of homocysteine to methionine. A defect in the enzyme MTHFR has previously been biochemically characterized and implicated in the development of hyperhomocyst(e)inemia[15,16] and coronary artery disease.[16] Recently, a missense mutation in the gene encoding MTHFR has been discovered.[17] The mutation, C677T, results when a cytosine residue at position 677 of the MTHFR gene is replaced by a thymine, introducing a HinfI restriction site within the gene. The C677T mutation results in a substitution of an alanine residue by valine in the enzyme, rendering the enzyme thermolabile and less active. Frosst et al. reported that in persons who were homozygous (+/+) for the C677T gene, MTHFR activity was reduced and tHcy concentrations were increased when compared with persons who were wild-type (-/-) or heterozygous (+/-).[17] Several investigators have indicated that there may be an interaction between the C677T mutation and plasma folate levels, such that homozygous persons manifest increased tHcy levels only when plasma folate levels are low.[17-21]

A number of studies have examined the association between the C677T genotype and risk for vascular disease with conflicting results.[22-25] Franchis el al.[24] and Kluijtmans et al.[25] reported a positive association between the C677T genotype and vascular disease. Kluijtmans et al.[25] reported that persons homozygous for C677T had an odds ratio of 3.1 (95% confidence interval (CI), 1.0-9.2) for cardiovascular disease. In contrast Wilcken et al.[22] and Schmitz et al.[23] found no association between genotype and risk for heart disease. The latter two studies concluded that their negative results may have been secondary to high folate levels in the populations under investigation.

Few studies have examined the prevalence of the C677T polymorphism in an African American population, a group which tends to have low plasma folate levels.[26] We used data from the Stroke Prevention in Young Women Study to determine the prevalence of the C677T genotype in both African American and white women. We also used the data to determine whether the C677T genotype was associated with tHcy concentration and whether environmental factors modified the association between genotype and tHcy concentration.

Methods

The Stroke Prevention in Young Women Study is a population-based case-control study examining risk factors for ischemic stroke in young women. The study area included all of Maryland (except for the far western panhandle), Washington D.C., as well as southern portions of both Pennsylvania and Delaware. The current analysis is limited to 123 healthy women aged 15-44 years without a prior history of stroke. These women were identified by random digit-

dialing. Trained interviewers went to each women's home to interveiw the women and to perform phlebotomy for tHcy. The participation rate was 85%.

Blood samples for tHcy concentration were drawn into Vacutainer EDTA tubes (Becton-Dickinson, Rutherford NJ), immediately placed on ice, transported to a central processing laboratory, and centrifuged at 4^0 C for 15 minutes. Plasma homocysteine is stable when whole blood is kept on ice for six hours before centrifugation.[27] Immediately after centrifugation the plasma samples were placed in cryogenic vials and frozen at -70^0 C until they were shipped on dry ice to the Oregon Regional Primate Center for analysis. Plasma tHcy concentration was determined by high performance liquid chromatography and electrochemical detection as previously described.[10,28,29] The analyses were run in duplicate, and the results were averaged.

C677T genotyping was performed as previously described.[30] Genomic DNA was isolated from 0.2 mL of frozen whole blood with a QiaAmp blood isolation kit (Qiagen, Chatsworth, CA) according to the manufacturer's recommendations and eluted with 200 µL of Tris HCl, pH 8.0. Five µL of purified DNA was used in a polymerase chain reaction containing primers (5'AAGGATGCCCATGTCGGTGCATGCCT 3' and 5' GAAGCAGGGAGCTTTGAGGCTGACCT) in a final volume of 50 µL to yield a 142 bp DNA product. One-tenth of the amplified DNA was digested to completion with restriction endonuclease Taq-I (Promega, Madison, WI) and electrophoresed in 10% polyacrylamide gel to generate three genotype-related patterns as previously described.[30] DNA specimens corresponding to all three genotypes that had been verified by DNA sequencing were included in the genotyping process as controls. Genotyping was performed blinded by laboratory personnel and each sample was examined two or more times with concordant results.

Potential effect modifiers for the association between genotype and tHcy concentration included age, education, high blood pressure, diabetes, body mass index (weight [kg]/height [m^2]), high blood cholesterol, cigarette smoking, and multivitamin use. Hypertension, high blood cholesterol, and diabetes status were determined by asking the participants if they had ever been told by a physician that they had the condition. Multivitamin use was assessed with the question "Are you taking multivitamins on a regular basis, and, if so, how many times per week?"

Because tHcy levels were positively skewed, we log transformed the homocysteine data; therefore the mean tHcy concentrations presented in this report are geometric means. We used Student's t-test and chi-square tests to compare unadjusted means and frequencies of selected characteristics between groups defined by race and genotype. All p-values are two-sided. In race-specific multivariate linear regression analyses, we used the SAS procedure Proc GLM[31] to determine whether the geometric mean tHcy concentration differed by genotype after stratification by selected environmental factors. The Proc GLM model adjusted for age, education, high blood pressure, diabetes, body mass index, high blood cholesterol, cigarette smoking and multivitamin use. We stratified all analyses by race in order to determine specific effect modifiers for African American and white women.

Results

We performed genotype analyses for 46 healthy African American and 77 healthy white women aged 15-44 years. African Americans were slightly younger than their white counterparts and more likely to have less than 12 years of education, to have high blood pressure, to have

diabetes, and to smoke cigarettes (Table 1). Mean body mass index also differed between the

race groups. High blood cholesterol and the regular consumption of multivitamins did not differ

between the two groups. Mean tHcy levels did not differ between African American and white

women (6.54 vs. 6.49 µmol/L respectively; p=0.9).

Despite the similarity in mean tHcy levels, the prevalences of the C677T genotypes

differed significantly by race (Table 2). None of the African American women were homozygous

for the C677T genotype. The C677T allele was significantly more prevalent among white than

African American women (34% vs 10%, respectively; p=0.01).

Among both African American and white women, mean age, educational attainment, and

the prevalence of diabetes, high blood cholesterol, and cigarette smoking did not differ by

genotype (Table 3). Among white women the prevalence of hypertension was significantly higher

for the homozygous genotype than for the heterozygous or wild-type genotype. A similar trend

was also noted among African American women (p=0.06). There was also a trend towards a

higher body mass index in the white women who were +/+ when compared with those who were

-/- or +/-. This trend was not found in African American women.

African American women who were +/- tended to have higher tHcy levels in comparison

to those who were -/- (6.9 µmol/L vs 5.3 µmol/L, respectively; p=0.10); no such trend was noted

among white women (Table 4). Across all genotypes, African American women who smoked

cigarettes or did not regularly consume multivitamins had a higher mean tHcy concentration than

those who did not smoke or who consumed multivitamins. There appeared to be an interaction

between genotype and tHcy level according to multivitamin use. Among African American

women who used multivitamins there was no difference in mean tHcy concentration levels

between genotypes (4.9 µmol/L -/-, 4.9 µmol/L +/-); however, among African American women who did not consume multivitamins, those who were +/- had significantly higher tHcy levels than those who were -/-. After stratifying on cigarette smoking, African American women who were +/- had higher tHcy levels than those who were -/-; however, this trend was not statistically significant. The lack of significant findings among African American women is likely to be secondary to the small sample size (N=46).

Among white women mean tHcy concentration did not differ significantly by genotype (6.0 µmol/L -/-, 4.5 µmol/L +/-, and 6.2 µmol/L +/+).(Table 4) Even after stratifying by multivitamin use and cigarette smoking we were unable to find a significant increase in tHcy concentration among white women who were +/+. In fact, we found slightly higher tHcy concentrations among white women who smoked and were -/- (8.1 µmol/L) when compared with those who were +/+ (7.6 µmol/L).

Discussion

This is one of the first studies to document the prevalence of the C677T polymorphism in a bi-racial population. The prevalence of the polymorphism differed markedly by race; in fact, we were unable to find any African American women who were homozygous for the polymorphism. Stevenson et al.[32] were also unable to find any African Americans that were homozygous for the C677T genotype (N=146); and they reported an allele prevalence of 11%, which is similar to the 10% we found. The findings from these two studies underscore the importance of documenting the prevalence of specific genetic factors in bi-racial populations.

In our study the frequency of the C677T allele was 34% among white women, which is comparable to previously reported prevalences of 36%-38%.[19-23] These studies also reported a prevalence of heterozygosity close to 50% and a prevalence of homozygosity close to 10%, demonstrating that the C677T allele is relatively common in healthy, white, female populations.

In African American women, the presence of only one allele was associated with a borderline significant increase in tHcy levels; among white women however, genotype was not associated with increased tHcy levels. The findings in white women are consistent with data from Schmitz et al.[23] who were also unable to demonstrate an association between genotype and tHcy. Christensen et al.[19] reported that genotype was not associated with tHcy concentrations among French Canadian adults with folate levels above the median. If white women in the current analyses had sufficiently high folate intakes this might explain our negative findings. A potential explanation for the race-genotype interaction concerning tHcy levels therefore might be racial differences in folic acid consumption. Data from the Third National Health and Nutrition Examination Survey, conducted between 1988-1994, indicate that African American women have substantially lower folate consumption rates than their white counterparts.[26] Unfortunately, the Stroke Prevention in Young Women Study did not include information on folate consumption or plasma folate concentration as part of the baseline assessment of study participants.

In our study, among white women the prevalence of hypertension was significantly higher among homozygous women than for other genotypes; and among African Americans, we noted a trend towards a higher prevalence of hypertension for the heterozygous subjects. We also noted a trend towards higher body mass index among white women who were +/+ when compared with those that were -/- and +/-. These findings are consistent with those from Wilcken et al.[22] who

reported modest associations between the C677T genotype and hypertension and body mass index. Wilcken et al. postulated that these associations may be secondary to an obesity-related gene on chromosome 1. While the results from this study and that of Wilcken et al. should be interpreted with caution, additional studies should examine the relationship between the C677T genotype, hypertension, and body mass index.

A number of environmental factors were found to be associated with mean tHcy concentration including the use of multivitamins and cigarette smoking. Across all genotypes, women who did not regularly consume multivitamins or did smoke cigarettes had a higher mean tHcy levels than women who consumed multivitamins or did not smoke. These findings are consistent with data from the Hordaland Study, in which both multivitamin use and cigarette smoking were found to be important correlates of tHcy concentration.[33]

Although non-significant, white women who smoked and were -/- had higher tHcy concentrations that those who were +/+ or +/-. This finding is consistent with data from both Christensen et al.[19] and Schwartz et al.[34] who reported that among adults with high folate levels there was a non-significant trend towards higher tHcy levels in persons who were wild type or heterozygous. Schwartz et al.[34] in a population of healthy women aged 18 to 44 years reported that among those with a folate concentration greater than 15.6 nmol/L, those who were wildtype or heterozygous had a higher mean tHcy concentration (9.18 µmol/L) than those who were homozygous (7.35 µmol/L; p=0.063). In addition, these findings may be secondary to homozygous persons being more responsive to increases in folate consumption when compared with heterozygous or wild-type persons.[21] Malinow et al. reported that among those who do not consume multivitamins, increases in folate consumption resulted in a 20.9% reduction in tHcy

concentration in homozygous persons compared with a 13.1% and 7.1% reduction in heterozygous and wildtype persons respectively.[21]

This study is subject to a number of potential limitations. First the number of African American and white women who underwent genotyping was small, this greatly limited our ability to find statistically significant results. However, despite this limitation, this is one of the largest studies to examine the prevalence of the C677T genotype in African Americans, and we still found important associations between genotype and tHcy concentration in African American women. Second, the study did not include information of folate, vitamin B12, and vitamin B6 levels, all important determinants of tHcy concentration.

Despite these limitations, the results from this study indicate that the prevalence of the C677T genotype is significantly lower in African Americans when compared with whites. In addition, the association between genotype and tHcy concentration appears to be complex and may differ based on a number of environmental factors, including cigarette smoking and the use of multivitamins. Additional studies examining the association between the C677T polymorphism and cardiovascular disease should include information related to each of these factors in order to further elucidate the complex relationships between genotype and risk for vascular disease.

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Table 1. Baseline characteristics of study participants. Stroke Prevention in Young Women Study.

	African American	White
Sample size	46	77
Mean age (years)	34.9	37.3
>12 years education (%)	45.7	57.1
High blood pressure (%)	19.6	11.7
Diabetes (%)	4.4	1.3
Mean body mass index (kg/m^2)	28.3	26.2
High blood cholesterol (%)	41.3	42.9
Cigarette smoking (%)	34.8	24.7
Multivitamin use (%)	39.1	41.6
Mean total homocysteine concentration (µmol/L)	6.54	6.49

Table 2. Genotype and allele prevalence stratified by race. Stroke Prevention in Young Women Study.

Genotype	Overall	African American	White
	N (%)	N (%)	N (%)
-/-	67 (54.5)	37 (80.4)	30 (39.0)
+/-	50 (40.7)	9(19.6)	41 (53.3)
+/+	6 (4.9)	0 (0.0)	6 (7.8)
Allele Frequency (%)			
-	68	90	66
+	32	10	34

Table 3. Baseline characteristics according to genotype and race. Stroke Prevention in Young women Study.

Characteristic	African American			Whites		
	-/-	+/-		-/-	+/-	+/+
Sample size	37	9		30	41	6
Mean age (years)	34.1	38.6		38.2	37.1	33.5
> 12 years education (%)	45.6	44.4		50.0	63.4	50.0
High blood pressure (%)	13.5	44.0[*]		10.0	7.3	50.0[**]
Diabetes (%)	2.7	11.1		3.3	0.0	0.0
Mean body mass index (kg/m^2)	28.2	28.4		25.2	26.4	29.5[*]
High blood cholesterol (%)	40.5	44.4		30.0	48.8	66.7
Cigarette smoking (%)	32.4	44.4		20.0	29.3	16.7
Multivitamin use	40.5	33.3		60.0	31.7	16.7[**]

[*]$0.05 < P \leq 0.1$.
[**]$P \leq 0.05$.

Table 4. Mean total homocysteine concentration (µmol/L) according to genotype and race.[*] Stroke Prevention in Young Women Study.

Characteristic	African American	White
Overall Genotype		
-/-	5.3	6.0
+/-	6.9[**]	4.5
+/+	- -	6.2
Multivitamin users Users		
-/-	4.9	5.3
+/-	4.9	4.3
+/+	- -	5.5
Non-users		
-/-	5.6	7.0
+/-	7.9[†]	5.0
+/+	- -	7.0
Cigarettes Non-smokers		
-/-	4.4	4.6
+/-	5.9	3.3
+/+	- -	5.0
Smokers		
-/-	6.5	8.1
+/-	8.0	5.7
+/+	- -	7.6

[*]Means are adjusted for age, education, high blood pressure, diabetes, body mass index, high blood cholesterol, cigarette smoking, and multivitamin use.
[**]$0.05 < P \leq 0.1$
[†]$P \leq 0.05$.

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